Amendments to the Specification:

Please amend the paragraph beginning on page 6, line 26, as follows.

In the event the third domain includes a polypeptide, the polypeptide can have random coil, α-helical or β-pleated tertiary structures. Polypeptides that form suitable flexible linters are well known in the art (*see, e.g.*, Robinson and Sauer, *Proc. Natl. Acad. Sci. USA* 95:5929-5934, 1998). α-helical linkers can impart additional rigidity. An example of a helical linker is provided by Pantoliano *et al.*, *Biochem.*, 30:10117-10125, 1991). Another helical linker is a polypeptide sequence which folds as a coiled-coil, especially a dimeric parallel or anti-parallel coiled-coil. In embodiments in which the first and second domains are identical, the third domain can be one strand of an anti-parallel coiled-coil. The therapeutic molecule in this embodiment is, therefore, a heterodimer. The degree of separation between the first and second domains can be modulated by varying the length of the coiled-coil. Further structural stability can be obtained by employing helical scaffold proteins, such as proteins containing multiple HEAT repeats (these repeats are so-named because they have been identified in four proteins, the names of which produce the acronym HEAT: Huntingtin, elongation factor 3 (EF3), the 65 kDa alpha regulatory subunit of protein phosphatase 2A (PP2A) and the yeast PI3-kinase TOR1), armadillo repeats, or tetratricopeptide (TPR) repeats (Groves and Barford, *Curr. Opin. Struct. Biol.* 9:383-389, 1999). Similarly, β-stranded structures can be a component of the third domain. Exemplary β-stranded structures include β-pleated tertiary structures and β-helix proteins (Jenkins *et al.*, *J. Struct. Biol.* 122:236-246, 1998).

Please amend the paragraph beginning on page 11, line 23, as follows.

As stated above, the "first" polypeptide is detectably labeled. Examples of detectable labels include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, and acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein

isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride, green fluorescent protein (or enhanced green fluorescent protein) and phycoerythrin; an example of a luminescent material is luminal; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive materials include ^{125}I, ^{131}I, ^{35}S, ^{32}P, and ^{3}H.

Please amend the paragraph beginning on page 12, line 21, as follows.

Huntington's disease (HD) is an autosomal dominant and progressive neurodegenerative disorder. It is associated with selective neuronal cell death that occurs primarily in the cortex and striatum and is characterized by a movement disorder, cognitive deficits, and psychiatric symptoms. HD is caused by an expansion of a CAG codon repeat in the first exon of the *huntingtin* (htt) gene, which encodes a 350 kDa protein of unknown function (Ambrose *et al.*, *Somat. Cell Mol. Genet.* 20:27-38, 1994). The nucleotide triplet CAG encodes the amino acid glutamine ("Gln" or "Q"). Thus, CAG repeats encode polyglutamine regions within ~~huntingtin~~ Huntingtin (and wherever they occur). The polyglutamine region of ~~huntingtin~~ Huntingtin from non-HD individuals contains about 8-31 consecutive glutamine residues. When the protein has more ~~then~~ than 37 consecutive glutamine residues, mild to severe HD results. The more severe cases of the disease exhibit up to about 68 glutamine residues. A juvenile onset form of HD is characterized by more widespread neuronal degeneration and is caused by expansions above approximately 65 repeats.

Please amend the paragraph beginning on page 14, line 12, as follows.

If the desired animal model is a mouse, numerous models of HD are available (*see*, *e.g.*, U.S. Patent No. 5,849,995; for a review, see Chicurel *et al.*, *Expression of Huntington's Disease Mutation in Mice* ~~at http://www.hdfoundation.org/PDF/hdmicetable.pdf)(2000)~~ and other information available through www.hdfoundation.org. The mouse HD cDNA sequence is deposited in GenBank as L23312 and L2313. Methods for generating transgenic mice are routine in the art (~~*See*~~ see, *e.g.*, Hogan *et al.*, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1994)). A mouse bearing a transgene comprising the HD gene and expanded CAG repeats has symptoms similar to the human disease.

Murine symptoms can include hyperactivity, circling, abnormal gait, tremors, learning deficits, hypoactivity, and hypokinesis. Neuropathological symptoms include general brain atrophy, progressive striatal atrophy, neuropil aggregates, inclusions in the striatum, reduced dendritic sprines, and cell loss in the ~~cortex,~~ cortex and striatum. Any of these behavioral or physiological deficits can be assessed in order to determine the efficacy of a given therapeutic agent of the invention. For example, the agent can be administered to a transgenic mouse model, generated as described above. The symptoms of a treated mouse can be compared to untreated mice at various times during and after treatment. In addition, treated and untreated mice can be sacrificed at various intervals after treatment, and the neuropathology of the brain can be analyzed. Thus, the efficacy of the treatment can be evaluated readily by comparing the behavioral symptoms, neuropathological symptoms, and clinical symptoms of treated and untreated mice.

Please amend the paragraph beginning on page 22, line 25, as follows.

Mammalian expression constructs: The polyglutamine expression constructs used in this study were described in detail in Kazantsev *et al.*, (*Proc. Natl. Acad. Sci. USA* 96:11404-11409, 1999). Spacers (referred to herein as "the third domain") containing two alpha-helical domains were amplified by PCR from full length TBP (~~Genbank~~ GenBank™ Accession No. M55654), as described in Kazantsev *et al.* (*supra*). Wild type TBP cDNA (~~Genbank~~ GenBank™ Accession No. M55654) was amplified from genomic DNA extracted from ~~cHeLa~~ HeLa cells, again, as described in Kazantsev *et al.* (*supra*). Desired TBP fragments were amplified by PCR with primers that introduced novel *Kpn*I and *Bgl*II restriction sites in the N-terminus and novel *Hind*III and ~~*BamH*II~~ *BamH*I restriction sites in the C-terminus. HD25Qmyc plasmid was used as a template. DNA fragments encoding H1/H2, H2/H3, and H3/H4 sequences were digested with *Kpn*I and *Hind*III subcloned in front of 25Q in ~~BlueScript~~ Bluescript™ vector. DNA fragments encoding HD25Q were isolated by digestion with *Kpn*I and ~~BamHI~~ *BamH*I and ligated in front of polypeptide fusion H/H 25Q digested with *Kpn*I and *Bgl*II. Resulting HD 25Q H/H 25Q polypeptide fusions were subcloned into a mammalian expression vector (pcDNA 3.1;

Invitrogen), using *Kpn*I and *BamH*I. Final clones were sequenced to verify the accuracy of molecular cloning manipulations. The mammalian expression vector, pBudC4 (Invitrogen) was also used. This vector permits expression of two polypeptides from the same plasmid.

Please amend the paragraph beginning on page 23, line 13, as follows.

Fluorescent analyses of transfected cells: Polyglutamine aggregation was assayed in ~~Cos-1, Cos-7,~~ COS-1, COS-7, NIH 3T3, 293, EcR-293, ~~eHeLa,~~ HeLa, NT-2, and PC-12 cell lines. Cells were grown on coverslips to 50% confluence and lipofected for two hours with ~~Transfectam~~ Transfectam™ reagent (Promega). Polyglutamine aggregation was assayed from 16 to 72 hours after transfection. Cells were fixed in 2% formaldehyde/0.1% triton-X100 for 10 minutes and incubated with primary mouse monoclonal anti-c-myc (Invitrogen) antibody ~~(1: 500)~~ (1:500) and secondary FluoroLink Cy3 (Amersham Life Science) antibody ~~(1: 2000)~~ (1:2000). Epifluorescent microscopy was performed on a Zeiss Axioplan II equipped with a Quantix CCD camera (Photometrics) and Spectrum imaging software (Scanalytics).

Please amend the paragraph beginning on page 27, line 21, as follows.

A *Drosophila* model expressing different polyQ peptides has been described (Marsh *et al.*, *Human Mol. Genetics* 9:13-25, 2000). In that model, expanded polyQ chains alone were intrinsically cytotoxic and caused neuronal degeneration ~~an early adult~~. PolyQ peptides, comprised of a glutamine tract +/- a myc/flag C-terminal epitope tag were placed under the control of an upstream activator sequence (UAS). Transgenic flies carrying a polyQ peptide were then crossed to flies expressing the yeast GAL4 transcriptional activator under tissue specific control. For these studies, polyQ peptides were expressed in all neurons from embryogenesis onward by an elav-GAL4 driver.